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Risk factors of having cholecystectomy for gallstone disease in a prospective population-based cohort study

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Original article

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Abstract

Background: The relationship between different lifestyle factors and the risk of having cholecystectomy for gallstone disease is not clear. We aimed to assess the association between anthropometric, lifestyle and sociodemographic risk factors and the subsequent risk of having cholecystectomy for gallstone disease during long-term follow-up in a defined population cohort.

Methods: Data from a large population-based cohort study performed from 1995 to 1997 was used (the second Norwegian Nord-Trøndelag health study; HUNT2). Following HUNT2, from 1998-2011, all patients operated for gallstone disease with cholecystectomy at the two hospitals in the county, Levanger Hospital and Namsos Hospital, were identified. A Cox proportional hazard model was used for multivariable risk analyses.

Results: The HUNT2 cohort included 65,237 persons (69.5 per cent response rate), aged 20 to 99 years. During a median follow-up period of 15.3 years (range 0.6-16.4 years), 1,162 cholecystectomies were performed. In the multivariable analysis, overweight individuals (body mass index [BMI] 25-29.9 kg/m^2) had 60 per cent increased risk of cholecystectomy compared with individuals with normal weight (BMI <25.0 kg/m^2). Obese individuals (BMI ≥ 30 kg/m^2) had a two-fold increased risk. Increasing waist circumference independently increased the risk of cholecystectomy. In women, current hormone replacement therapy (HRT) increased the risk, while hard physical activity and higher educational level were associated with reduced risk of cholecystectomy.

Conclusion: High BMI and waist circumference increased the risk of having cholecystectomy for both sexes. In women, the risk was increased by HRT and decreased by hard physical activity and higher educational level.

Introduction

In Europe and North-America, gallstones are the leading cause of inpatient admissions for gastrointestinal diseases[1] and cholecystectomy for gallstone disease is one of the most common elective operations performed[2]. The cholecystectomy rates in North-America increased during the 1990s, probably explained by increased incidence of cholelithiasis, an increased frequency of symptomatic gallstone disease, improved diagnostic expertise and a lowered threshold for surgery[1]. However, in the late 1990s the cholecystectomy rate stabilized following the introduction of the laparoscopic technique[3-5], as also demonstrated in Europe[6-8]. In Nord-Trøndelag County, Norway, the cholecystectomy rates increased during the years following introduction of laparoscopic surgery, from 6.2 per 100,000 person years in 1990-1992 to 10.0 in 1998-2003 and has remained stable since[7].

The estimated prevalence of gallstones in Europe and North-America is 5-25 per cent and 50-80 per cent of patients are asymptomatic[1, 8]. In addition, the prevalence of gallstone disease in a population appears to have little influence on the incidence of gallbladder surgery[9]. The presence of asymptomatic gallstone differs from symptomatic gallstone disease resulting in laparoscopic surgery. Several studies have assessed risk factors for gallstones[10-12]. However, these studies focused on the risk of gallstone formation and did not have symptomatic disease or cholecystectomy as an endpoint. The subsequent risk factors of having a cholecystectomy performed are less well investigated.

Seven out of ten cholecystectomies are performed in women, both in the past and present era[13]. Overweight, parity, hormone replacement therapy and use of contraceptives have been suggested as risk factors for cholecystectomy[12, 14-16]. However, most previous studies have been performed in selected groups of patients, mainly postmenopausal women, and not in an unselected general population. Thus, the aim of this study was to examine lifestyle related risk factors of having a

cholecystectomy in a large and unselected prospective population-based cohort study.

Subjects and Methods

Study population

The study base was the population of Nord-Trøndelag County, Norway (*Figure 1*). The population structure of Nord-Trøndelag is stable and representative for Norway, except for slightly lower income and the absence of larger cities[17]. During 1995-1997, all residents in Nord-Trøndelag aged 20 years and older were invited to participate in the second wave of the Nord-Trøndelag health study (HUNT2), a survey consisting of written questionnaires on health related topics, physical examinations and blood sampling[18, 19].

Inclusion and exclusion criteria

All residents above 20 years of age living in Nord-Trøndelag County, Norway, were invited to participate in the HUNT2 study during 1995-1997. Those who took part in the study where included if they had completed the questionnaires and anthropometric measurements. Surgery for gallstone disease was only performed at the two hospitals in the county, Levanger Hospital and Namsos Hospital. All patients operated for gallstone disease were included, identified using surgical codes for cholecystectomy in the patient administrative system at the hospitals during 1998-2011. Patients who had been operated for gallstone disease with cholecystectomy and had participated in HUNT2 were included as 'cases' and the remaining HUNT2 participants were included as 'controls'. Patients who had a cholecystectomy during the period 1990-1997 (preceding HUNT2), operated for malignant disease or residing outside the county were excluded.

Informed consent

The participants in HUNT gave written informed consent for medical research, including linkage to patient records at the hospitals.

Risk factors and definitions

A full description of the questionnaires and measurements is given at the HUNT homepage[18-20]. From HUNT2 we used information from questionnaires on physical activity, parity, contraceptive medication, hormone replacement therapy and data on anthropometric measurements. Height, weight and waist circumference were measured with standardized methods by qualified personnel.

Based on the World Health Organization's (WHO's) classification, body mass index (BMI) was calculated and individuals were categorized as normal weight (BMI <25.0 kg/m^2), overweight (25-29.9 kg/m^2) or obese (≥30 kg/m^2)[21] . Waist circumference was categorized according to WHO in three categories for each sex: in men normal (<94 cm), increased (94-101 cm) and substantially increased (≥102 cm); and in women normal (<80 cm), increased (80-87 cm) and substantially increased (≥88 cm)[21].

Statistical analysis

The analyses were performed using IBM SPSS Statistics 22 (SPSS Inc., Chicago, Illinois, USA) and StatXact 9 (Cytel Inc., Cambridge, Massachusetts, USA). The study endpoint was cholecystectomy for gallstones. Observation time was measured from the date of participation in HUNT2 until date of admission for cholecystectomy, death, moving out of Nord-Trøndelag

County or end of study (December 31, 2011), whichever occurred first. Women and men were analysed separately. Proportions were compared using the unconditional z-pooled test, which is the unconditional version of the Pearson Chi-square test. The exact Cochran-Armitage test was used to test for trends in proportions. A Cox' proportional hazard model was used for multivariable analysis of risk factors for cholecystectomy for gallstone disease. Estimates of hazard ratios (HRs) were accompanied by 95 per cent confidence intervals (95 per cent c.i.). All tests were two-tailed and statistical significance set at p-values <0.050.

Results

Participation

In HUNT2, 65,237 persons attended (69.5 per cent response rate). Of these, 63,259 persons were included in the present study and 1,988 persons were excluded after not answering the questionnaires. A flowchart of patient inclusion and exclusion is shown in *Figure 2*. In total, 1,841 persons were operated, of whom 1,162 (63.1per cent) participated in HUNT2. The included participants contributed 957,403 person-years of follow-up from 1996 to 2011 and were followed up for a median of 15.3 years (range 0.6-16.4 years). The 511 patients who had cholecystectomy during the period from 1990 until their participation in HUNT2 were excluded from the study.

Baseline characteristics

The mean age at start of the cohort was 50 years (range 20-99 years) and 33,267 (53 per cent) were women. Cholecystectomy was performed in 813 (2.4 per cent) of 33,267 women and 349 (1.2 per cent) of 29,982 men during follow up. The mean age at operation was 57 years (range 26-90 years) in women and 62 years (range 28-90 years) in men. The sex-specific distribution of baseline characteristics according to cholecystectomy is shown in *Table 1*.

Risk of having cholecystectomy

The rate of cholecystectomy was highest among the middle aged (40-60 years) in both sexes. There was an increased rate of cholecystectomy with increasing BMI and increasing waist circumference in both women and men. In women, the rate of cholecystectomy was lower among those with a higher educational level, while no such relationship was found in men. In both

genders, the rate of cholecystectomy was lower among those who had reported hard physical activity of more than one hour per week. The rate of cholecystectomy was higher with increasing parity and with use of hormone replacement therapy, while use of oral contraceptives showed no association with the rates of cholecystectomy.

Among the 679 persons who had been operated but did not participate in HUNT2 (excluded from the present study), 501 (74 per cent) were women and the mean age at operation was 38 years (range 20-99), compared to 53 per cent women and a mean age at operation of 60 years (26-90) among those included in the present study. Median time to surgery was 7.9 years (range 0.07-16.0 years) for women and 8.2 years (range 0.09-16.2 years) for men.

Associations between risk factors and cholecystectomy

The results for each sex separately are shown in *Table 2* (univariable analyses) and *Table 3* (multivariable analysis). In women, the risk of cholecystectomy decreased with higher age. In men, however, the risk increased with increasing age up to 70-79 years. In both sexes, the risk of cholecystectomy was higher with increasing BMI in a dose-response relationship. Increasing waist circumference, likewise, independently increased the risk of cholecystectomy in a dose-response relationship. Among women, university level education reduced the risk of cholecystectomy. This association was not present in men. In the univariable analysis, hard physical activity of more than one hour per week was associated with reduced risk of cholecystectomy in both sexes. This association was retained in women in the multivariable analysis, but was no longer statistically significant in men. In the univariable analysis, parity was associated with increased risk of cholecystectomy in a dose-response relationship. In the multivariable analysis, the association attenuated. In women who ever have used hormone replacement therapy, the risk of cholecystectomy increased compared with never user. The use of

contraceptive medication was not associated with the risk of cholecystectomy (results not shown).

Sensitivity analysis

As some variables had substantial number of participants with missing values (*Table 1*), we ran the regressions using a missing value category for all variables with missing. As the estimates did not change substantially and the conclusions remained the same, we chose not to include the missing value category in the final analyses (results not shown).

Discussion

In this population-based cohort study with a median observation time of 15 years, overweight and obese persons had 1.5 to 2 times increased risk of having cholecystectomy for gallstone disease compared to persons with normal weight. Increased waist circumference was independently associated with risk of cholecystectomy. In women, hormone replacement therapy increased the risk, while hard physical activity beyond one hour per week and higher educational level were associated with a reduced risk of cholecystectomy. With increasing parity, there was a trend towards increased risk of cholecystectomy. Contraceptive medication showed no association with the risk of cholecystectomy. Increasing age decreased the risk of cholecystectomy for gallstones in women, but increased the risk in men.

The results are in agreement with a limited number of other population-based cohort studies of lifestyle related risk factors related to symptomatic gallstone disease or cholecystectomy[16, 22-24]. Among these studies, only Tsai et al. used cholecystectomy as endpoint, but their study was limited to women[16]. They found that abdominal circumference and waist to hip ratio were associated with an increased risk of cholecystectomy, independent of BMI. Symptomatic gallstone disease was used as endpoint by Hou et al., but they also limited the study to women[22]. They found that regardless of adiposity level, being physically active reduced the risk of gallstone disease. Stender et al found an association between elevated BMI and increased risk of symptomatic gallstone disease, which was most pronounced in women.[23]. Banim et al. concluded that an association between physical activity and the risk of gallstone disease may be causal as there are consistent experimental and epidemiological data regarding a protective effect of physical activity in both sexes[24]. In the present study we found an association between elevated BMI and waist circumference and increased risk of cholecystectomy for gallstone disease, and negative (protective) association with physical activity, at least for women who did hard physical

activity at least one hour per week. However, the conclusions are based on self-assessment of physical activity and must therefore be interpreted with this in mind. Previous studies have reported that hormone replacement therapy is a risk factor for gallstones and cholecystectomy[10, 12, 25], as in the present study. A possible increased risk of cholecystectomy in women with many children and in those taking oral contraceptives has been discussed in previous reports[11, 15, 26, 27], but this was not confirmed in the present study.

Laparoscopic cholecystectomy was introduced in Nord-Trøndelag in 1992 and since 1998 (the baseline of our study) laparoscopic cholecystectomy was the standard procedure. Open cholecystectomies were performed only in advanced cases and represented only around 10 per cent of the procedures. The incidence of cholecystectomy in Nord-Trøndelag increased from 6.2 per 100,000 person years in 1990-1992 to 10.0 in 1998-2003 and has been stable since[2]. This increase coincided with an increase in obesity documented during this time in the same county by the three HUNT studies[28]. Similar, the cholecystectomy rates increased during the 1990s in North-America, parallel with the increase in obesity and the rate stabilized in the late 1990s following the introduction of the laparoscopic technique[3-5].

The population-based design with a large sample size, long observation time and completeness of cholecystectomy detection strengthened this study. It is also a clear advantage that the HUNT2 study utilized objective standardized measurements of height, weight and waist circumference performed by qualified personnel. The population structure of Nord-Trøndelag County is relatively stable, which makes it possible for accurate long-term follow-up.

A weakness of study is the lack of records of patients operated for gallstone disease before 1990. These patients, who could in theory potentially have had a cholecystectomy, were treated as controls in the current study, together with all patients who were truly had no operation prior to 1990. However, due to the large number of controls, the effect of including persons with

cholecystectomy before 1990 would be small and the effect of this would be to attenuate the risk estimates. Those who had been operated but did not participate in HUNT2 had a mean age 22 years younger than those included in HUNT2. This difference in age may add to the uncertainty of the results of the present study, but we adjusted for age in the multivariable analysis. Whether the controls had surgery elsewhere or not is uncertain. However, in Nord-Trøndelag almost all health care is provided by universal health coverage in the county of residence and private hospitals and surgery outside the public hospitals is not common. We do not know if the participants used as controls in this study had gallstones. However, gallstones per se are not an indication for cholecystectomy, which was the outcome of this study. Only about 10 per cent of persons with gallstones develop symptoms that require surgery[14]. Before the era of laparoscopic surgery the indication for cholecystectomy was one or more episodes of cholecystitis and gallstone-related pain. However, after the introduction of laparoscopic surgery in the later years, many have been offered surgery only after episodes of gallstone colic[7]. In HUNT2, 32 per cent of the population did not participate. A non-participants study done after HUNT3, showed that the population not captured were the youngest (20-39 years of age) and the oldest (80+) residents. More men than women did not participate and the non-participants had lower socioeconomic status and higher mortality and prevalence of several chronic diseases[19]. This must be kept in mind when generalizing the results.

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